IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Julie Straub, Howard Bernstein, Donald E. Chickering, III, Sarwat Khattak, and Greg Randall

Serial No.: 09/706,045 Art Unit: 1617

Filed: November 3, 2000 Examiner: E. Webman

For: *POROUS DRUG MATRICES AND METHODS OF MANUFACTURE THEREOF*

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 C.F.R. § 1.131

Sir:

We, Julie Straub and Howard Bernstein, hereby declare that:

1. We are co-inventors of the above-identified application.

2. We conceived of and reduced to practice a method of forming microparticles that contain a diagnostic agent, which was subsequently described in U.S. Patent No. 6,565,885 to Tarara et al. This method involves spray drying a feed stock containing the diagnostic agent, a surfactant and a blowing agent. We conceived of and reduced to practice this method prior to September 29, 1997, as demonstrated by the attached copies of pages from a laboratory notebook (Exhibit A).

3. As noted in Exhibit A, the feed stock to the spray drying apparatus contained ammonium acetate, lecithin, (poly(ethylene glycol)-co-poly(lactide-co-glycolide) (75:25), D,L-

poly(lactide), and air. This composition was emulsified using a VirTis homogenizer to form an emulsion, which was then spray dried using a small-scale lab spray dryer (see Exhibit A, page 14). The resulting microparticles had diameters ranging from 1-20 microns and were hollow with internal central-like voids containing the air bubble, as demonstrated by transmission electron microscopy (see Exhibit A, page 116). These microparticles were echogenic (see Exhibit A, page 105, injection 7).

4. I declare that all statements made herein of my own knowledge and belief are true and that all statements made on information and belief are believed to be true, and further, that the statements are made with the knowledge that willful false statements are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 1-22-04

Julie Straub

Date: 1-22-04

Howard Bernstein

1517614_v1

EXHIBIT A

14 **TITLE**

Work continued from Page 13 HenT.Bl 8/29/95

PROJECT NO.

BOOK NO. [redacted]

Investigator(s): H.Brook
Notebook/page #:
Date: [redacted]
Microsphere lot #: 5? 3?1-11

Microsphere Production

Process Room Conditions

Room Temp.:	22°C
Room Humidity:	51.5% RH

Polymer Preparation

Polymer type 1:	PEG-PLGA
Source & Lot no.:	BPI, Lot # 904-14-19
Mass (g):	3.6 g
Polymer type 2:	D,L-PLA
Source & Lot no.:	BI, Lot # 310 3?5
Mass (g):	3.6 g
Solvent Type:	MeCl₂
Source & Lot no.:	EM, lot no 3506B
Volume:	780 mls
Surfactant type:	Lecithin
Surf.(Mat)/Vol.:	35 mg
Dissolution Meth.:	Stir bar
Dissolution Temp.:	Room temperature
Dissolution Time:	12:55
Excipient 1:	H_2O
Source & Lot no.:	House DI
Amount, g/ml:	3 mls
Comments: Dissolve ammonium acetate in water as follows: 10.8 g in 3 mls of H_2O. Add soln to polymer solution.	

Aeration Methodology

Sonication:	None
Horn type:	
Frequency:	
Power:	
Temperature:	
Time:	
Time until spray:	
Sparging:	None
Gas type:	
Gas pressure:	
Temperature:	
Time:	
Time until spray:	
Homogenization:	VIRTIS
Blade type:	macro ultra-fine generator
Time:	minutes 1:13
Speed:	10,000 RPM
Temperature:	Ice bath
Time until spray:	~ 3 minutes
Comments:	

Spray Conditions

Cleaning Proc.:	Kaumou solutions Michrolene nozzle
Nozzle type:	0.7mm standard, cap/B
Gas Pressure:	95psi
Gas Flow rate:	600 L/h
Gas type:	Air, medical grade
Feed Flowrate:	112 rpm
Inlet Temp.:	50°C
Start Time:	1:16
Finish Time:	1:48
Mass Recov'd:	1229-1082 = 1.47
Yield (%):	22%

Process Conditions:

	Start 1:17	Middle 1:37	Finish
Outlet Temp.:	29°C	31°C	29°C
Filter vacuum:	-40 mbar	-10 mbar	-38 mbar

Comments:
Did not have inlet tube as I had done of a previous batch.

Drying Methodology

Type:	Lyophilization, VIRTIS Genesis 6
Total dry time:	start 2:30 pm 8/29, end time 8/30
Mass recovered:	Wt. before 15.485 - 14.?1 = 1.734
Yield (%):	1.482 g ... 25%
Comments: Froze in Etoh/dry ice bath. Lowered from dryice at 2:35 Pm 8/29, 8pm, weight = 1.249. Placed back on lyophilization. Removed from lyophilizer at 10.51 AM, 8/30	

Sieving Methodology

Room Temp.:	
Room Humidity:	
Screening Time:	
Screen sizes:	
Screen type:	
Product recovered:	
Yield (%):	
Comments:	

HenT.Bl [redacted]

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DATE [redacted]

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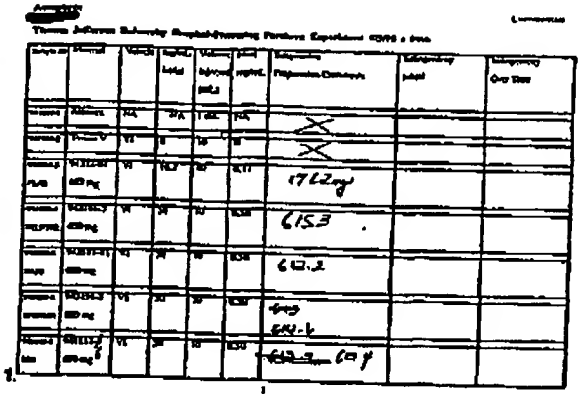
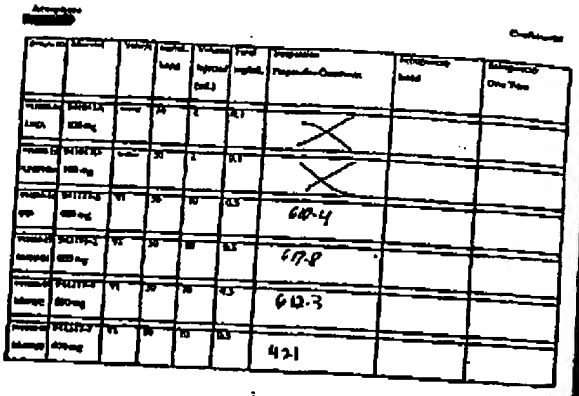
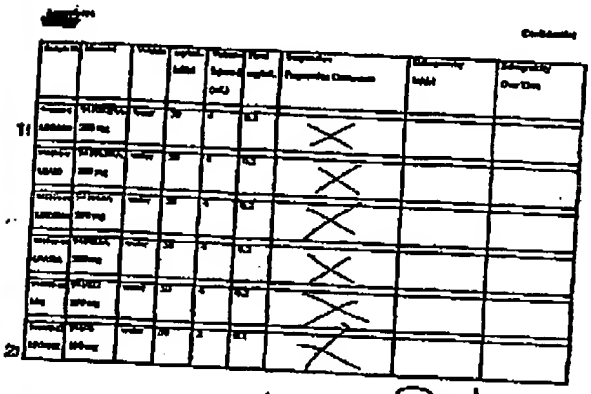
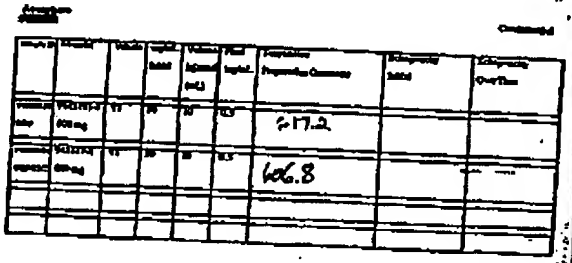
DATE [redacted]
WITNESS
DATE

80 TITLE TJU Study For [redacted] PROJECT NO









Samples weighed by Howard in Dry Box on [redacted]. All but the 94082 and 94083 samples sent to Fryxell on [redacted] by Airborne on dry ice / gel pak

SCIENTIFIC IMAGERY PRODUCTIONS CHICAGO IMAGE Made in USA

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116

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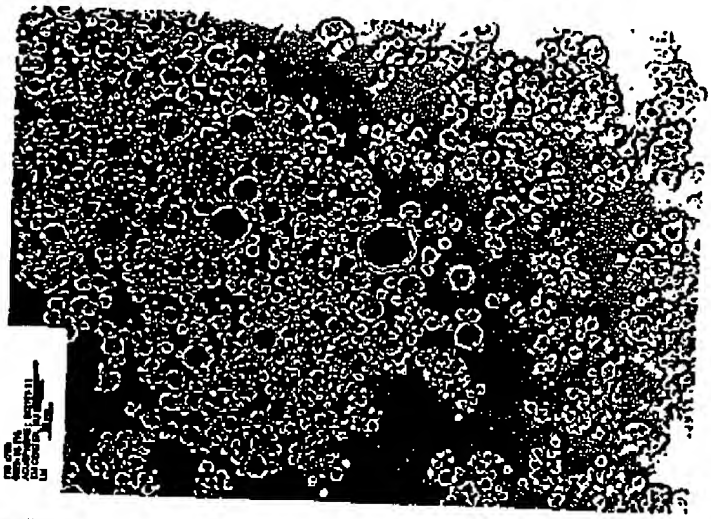

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DATE

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106 TITLE PROJECT NO

[illegible]

Acceptance [redacted]

Notes

All samples will be prepared by vortexing and sonication.

All samples will be preweighed in 20 mL scintillation vials. Empty 20 mL scintillation vials will be brought.

Saline (0.9%) will be used instead of water for the bulk diluent in the pumping system. Preweighed samples of 16.2 g of NaCl will be brought out, and diluted to 1800 mL with water in a bottle. Two such bottles will be sent to [illegible]. A total of 20 NaCl vials will be brought.

Vehicle 1 = 0.5% Tween 20, 3% glycerol ← never used

Vehicle 2 = 0.5% F127, 34.6 mg/mL mannitol

1) System essentially same as [redacted] experiment, except 500mL saline in [illegible]
2) Vehicle 2 (VF) was used
3) [illegible] did the entire study
4) After injection of sample, sample was stirred, flow rate was then increased to 500-800mL/min until echogenic material detected by the oscilloscope, Flow rate then dropped to 100-200 mL/min.
5) The "latex window" moved dramatically with each pulse
6) Tubing was manipulated to remove bubbles. At least once (prior to injection 9) this resulted in change of alignment. At that one detected time, the transducer was realigned.
7) Cleaning procedures: (1) water pumped to remove all material, then saline pumped in (2) water emptied, saline added + pumped through.

(2) System pumped dry, saline pumped in

[redacted]

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TITLE

Work [illegible]

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105

Acusphere [redacted]

Confidential

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Injection #	Sample ID/Material (Modified, etc.)	Suspension Preparation	Echogenicity Initial	Echogenicity Over Time	[illegible]
1	Albunex 0.5	NA ([illegible])	none — [illegible]		NO
2	Albunex 0.5 mL	NA ([illegible])	[illegible]		NO
3	Albunex 0.7	"	echogenic		[illegible]
4	Albunex (F) [illegible]	[illegible] 8.2 / V in [illegible] mL	not echogenic		NO
5	3-VF-12 mL	V/S2/V [illegible]	v. little echogenic	too little to follow	yes
6	4-VF-12 mL	V/S1/V/S/V [illegible]	a little echogenic [illegible]	decreases over 1 min	yes
7	5-VF-12 mL	V/S1/V [illegible] 10 mL	echogenic (bulky)	~ [illegible] min	[illegible]
8	94050-9 ([illegible])	Sh 4 mL	echogenic [illegible]	< 1 min	yes
9	94050-11 ([illegible])	Sh 4 mL	a little [illegible]	< 1 min	NO
10	Albunex [illegible] mL	NA ([illegible])	slightly echogenic [illegible]	[illegible]	yes
11	94050-[illegible]	V/S1/V/S1/[illegible]	[illegible]	not long	[illegible]
12	18-VF-12	V/S/V [illegible]	slightly echogenic	1-2 min	yes
13	19-VF-12	V/S1/V/S1/[illegible]	none		yes
14	13-2 mL H2O	Sh 2 mL	echogenic [illegible]	1-2 min	yes
15	15-2 mL H2O	Sh 2 mL	echogenic [illegible]	1-2 min	yes
16	8 (2 mL H2O)	Sh 4 mL	echogenic [illegible]	1-2 min	yes

Acusphere [redacted]

Confidential

Injection #	Sample ID/Material	Suspension Preparation	Echogenicity Initial	Echogenicity Over Time	
	.55				
17	5 ([illegible])	[illegible] 1 mL V/S1/V/S/V	slightly echogenic [illegible]	gone 1-2 min	yes
18	6-VF-12	a few flakes [illegible] V/S1/V/S1/V	none		[illegible]
19	8i-VF-12	a few flakes V/S1/V/S1/V	none		NO
20	16-VF-12	a few flakes V/S1/V/S1/V	slightly echogenic	< 1 min	yes
21	10 [illegible]	Sh 4 mL	very very slight	< 1 min	NO
22	7-[illegible]	Sh 4 mL	very very slight	< 30s	[illegible]
23	21-VF-12	V/S1/V/S1/V 10 mL	very very slight	< 30s	[illegible]
24	14 2 mL H2O	Sh 2 mL	none		NO
25	17-VF-12	V/S2/V 10 mL	none		NO
26	Albunex 0.2	NA	little echogenic		
27					
28					
29					
30					
31					
32					

Study Run at TJU on [redacted]

SCIENTIFIC BINDERY PRODUCTIONS CHICAGO [illegible] Made in USA

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